XII.

CONTRIBUTIONS FROM THE CHEMICAL LABORATORY OF HARVARD COLLEGE.

ON THE ETHERS OF URIC ACID.

SECOND PAPER.

DIMETHYLURIC ACID.

By H. B. HILL AND C. F. MABERY.

DIMETHYLURIC acid is formed when diplumbic urate is heated with methyl iodide according to the general method which one of us has already described * for making the monomethyl compound. The preparation of considerable quantities of pure substance by this method is, however, a matter of some difficulty, and we have found that a close attention to details is necessary to insure success.

The diplumbic urate which we used at first was made according to the directions of Allan and Bensch,† by precipitating a boiling solution of plumbic nitrate with dipotassic urate purified by alcohol. Although we heated this lead salt with an excess of methyl iodide at various temperatures (100° to 170°) for different lengths of time (five to ninety hours), we could not succeed in obtaining from it a product which did not contain quite a large percentage of the monomethyl ether. We therefore attempted to effect the separation of the monomethyl and dimethyl compounds by fractional crystallization, or by methods based upon differences in the behavior of their salts ; but we were unable to find a method which was at all satisfactory, and, after many experiments, convinced ourselves that it was necessary to obtain from the first a product essentially free from the monomethyl compound.

After a long series of experiments which need not be described in detail, we found that such a product could be obtained from a lead

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* These Proceedings, Vol. XII. p. 27.
† Ann. Chem. u. Pharm., lxv. 191.

salt made by precipitating with the diplumbic urate a small amount of plumbic hydrate. We have made no experiments to show how small this quantity of plumbic hydrate can be made with safety, as it seemed a matter of little importance. In preparing the lead salt we dissolved uric acid in a potassic hydrate solution of known strength, using twenty per cent more potassic hydrate than was theoretically required to form the dipotassic urate, and poured this alkaline solution into a boiling dilute solution of plumbic nitrate. After washing the bulky precipitate with hot water we usually washed with alcohol, and finally with a little ether; partly to facilitate the drying, and partly because the lead salt was in this way obtained in a much more compact and convenient form. After drying at 100° the salt was well powdered and dried at 160°.

In order to insure complete decomposition of the lead salt, which evidently is essential to prevent the formation of monomethyluric acid, we have found it necessary to take a slight excess of methyl iodide, to dilute it with an equal weight of ether, and, after mixing thoroughly with the lead salt, to heat for twenty hours at 165°. We also have found it advantageous to allow the tube to cool after heating for twelve to fifteen hours, and to mix the contents thoroughly by shaking before heating further.

After distilling off the ether and the slight excess of methyl iodide, the solid product of the reaction is extracted with boiling water, and the lead precipitated by hydric sulphide. The solution filtered boiling hot deposits on cooling crystals of dimethyluric acid which may be purified by recrystallization from hot water. In this way we have obtained about fifty per cent of the theoretical yield of well crystallized product apparently pure. Since monomethyl and dimethyluric acids differ in the amount of carbon they contain only by 3.29 per cent, it is evident that the absolute purity of our product could not be determined by analysis.

Dimethyluric acid crystallizes usually in slender oblique prisms, often concentrically grouped, which contain a molecule of crystal water. From saturated solutions where crystallization takes place at a high temperature we have not unfrequently obtained small, compact, pointed prisms, which contain less water and very possibly are anhydrous. The behavior of both of these forms to polarized light shows that they belong to one of the oblique systems. The acid begins to turn brown when heated to about 340°; at higher temperatures it melts, with decomposition and partial sublimation. It is quite soluble in boiling water, sparingly soluble in cold water, still less so in

alcohol, and insoluble in ether. Concentrated sulphuric and hydrochloric acids dissolve it readily, and deposit the greater portion upon dilution.

The slender oblique prisms in which methyluric acid ordinarily crytallizes contain one molecule of water when dried in vacuo over sulphuric acid.

0.6067 gr. lost at 160° 0.0511 gr. $H_2O = 8.49\%$.

The formula $C_5H_2(CH_3)_2N_4O_3 . H_2O$ requires 8.41%.

The crystals of the second form were obtained for analysis by evaporating a saturated solution of the acid upon the water-bath, and filtering hot. Although our determinations agree closely with the amount required for a half-molecule of water, it is not impossible that the loss in weight is due to hygroscopic moisture, as was the case with the monomethyl acid.

I. 0.4547 gr. substance dried in vacuo lost at 160° 0.0196 gr. $H_2O = 4.31\%$.

II. 0.2651 gr. lost 0.0114 gr. $H_2O = 4.30\%$.

The formula $C_5H_2(CH_3)_2N_4O_3 . \frac{1}{2}H_2O$ requires 4.39%.

The composition of the substance dried at 160° was determined by the following analyses : —

I. 0.2747 gr. gave 0.1097 gr. H_2O and 0.4291 gr. CO_2.
II. 0.2022 gr. gave 0.0789 gr. H_2O and 0.3167 gr. CO_2.
III. 0.1393 gr. gave 0.0557 gr. H_2O and 0.2185 gr. CO_2.
IV. 0.3521 gr. gave 86 cc. nitrogen at 16° and 756.5 mm. pressure.

	Calculated for $C_5H_2(CH_3)_2N_4O_3$	1.	2.	3.	4.
C	42.85	42.60	42.72	42.78	
H	4.08	4.44	4.34	4.44	
N	28.57				28.21

The solubility in boiling water was determined by filtering a boiling saturated solution through a hot-water filter into weighed flasks. After cooling, the flasks were weighed, the contents transferred to platinum dishes, evaporated to dryness, and the residue dried at 165°.

I. 54.2110 gr. solution left 0.2043 gr. residue.
II. 57.8596 gr. solution left 0.2940 gr. residue.

The boiling saturated solution contains the following percentages : —

1.	2.
0.5152	0.5081

To determine the solubility in cold water a hot solution was kept at 20° for four hours with occasional stirring. The solution was then filtered into weighed platinum crucibles, evaporated to dryness, and the residue heated at 160°.

I. 35.6147 gr. solution left 0.0189 gr. residue.
II. 25.2221 gr. solution left 0.0134 gr. residue.
III. 21.9260 gr. solution left 0.0116 gr. residue.

The solution saturated at 20° contained in percentages: —

1.	2.	3.
0.0531	0.0532	0.0529

Taking the mean of these results dimethyluric acid requires for solution 195.2 parts boiling water and 1885.3 parts of water at 20°.

An aqueous solution has a slight acid reaction, and decomposes carbonates on heating. A solution in sodic or potassic hydrate is not precipitated by carbonic dioxide. From concentrated cold solutions it is precipitated by stronger acids in a gelatinous form; from more dilute solutions it separates in crystals.

SALTS OF DIMETHYLURIC ACID.

Dipotassic dimethylurate.

$$K_2C_5(CH_3)_2N_4O_3 . 4 H_2O.$$
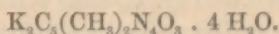
Dimethyluric acid was dissolved in an excess of a dilute solution of potassic hydrate, the clear solution boiled for several minutes, and about ten volumes of alcohol added. The crystalline precipitate, which separated on standing, was filtered off rapidly by the pump, washed with alcohol, and dried in vacuo over sulphuric acid and potassic hydrate. This salt crystallizes in fine silky needles, which are very soluble in water. It absorbs carbonic dioxide very rapidly from the air, probably forming the monopotassic salt.

To determine the water of crystallization the salt was heated in a current of dry air, free from carbonic dioxide.

0.8079 gr. salt dried in vacuo gave 0.1662 gr. H_2O = 20.57%
Calculated for $K_2C_5(CH_3)_2N_4O_3 . 4 H_2O$ . . . 20.92%

0.3198 gr. anhydrous salt gave 0.1766 gr. KCl . K = 28.95%
Calculated for $K_2C_5(CH_3)_2N_4O_3$ 28.73%

Monopotassic dimethylurate.
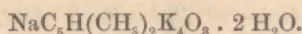
$$KC_5H(CH_3)_2N_4O_3 . 1\frac{1}{2} H_2O.$$
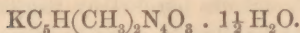
Potassic carbonate, in slight excess of the theoretical amount, is added to the acid suspended in boiling water. The solution is boiled for some time, and the salt precipitated by adding about ten volumes of alcohol. It is then filtered, washed with alcohol, and dried in vacuo over sulphuric acid. The salt crystallizes in branching needles, which are quite soluble in water.

0.2540 gr. salt dried in vacuo gave 0.0278 gr. H_2O $=$ 10.94%
   Calculated for $KC_5H(CH_3)_2N_4O_3 . 1\frac{1}{2} H_2O$ . .   10.35%
0.2180 gr. anhydrous salt gave 0.0702 gr. KCl . K $=$ 16.88%
   Calculated for $KC_5H(CH_3)_2N_4O_3$ 16.70%

Disodic dimethylurate.

$$Na_2C_5(CH_3)_2N_4O_3 . 4\frac{1}{2} H_2O.$$
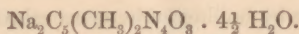
This salt is precipitated from a sodic hydrate solution of the acid by alcohol in the same way as the dipotassic salt. It crystallizes in needles much larger than those of the corresponding potassic salt.

0.3064 gr. salt dried in vacuo gave 0.0780 gr. H_2O $=$ 25.46%
   Calculated for $Na_2C_5(CH_3)_2N_4O_3 . 4\frac{1}{2} H_2O$ . .   25.23%
0.2234 gr. anhydrous salt gave 0.1074 gr. NaCl . Na $=$ 18.91%
   Calculated for $Na_2C_5(CH_3)_2N_4O_3$ 19.17%

Monosodic dimethylurate.

$$NaC_5H(CH_3)_2K_4O_3 . 2 H_2O.$$

This salt was made in the same way as the monopotassic salt. It forms microscopic needles which are more soluble in water than the potassic salt.

0.5327 gr. salt dried in vacuo gave 0.0798 gr. H_2O $=$ 14.98%
   Calculated for $NaC_5H(CH_3)_2N_4O_3 . 2 H_2O$. . .   14.18%
0.3069 gr. anhydrous salt gave 0.0638 gr. NaCl . Na $=$ 10.17%
   Calculated for $NaC_5H(CH_3)_2N_4O_3$ 10.54%

Dibaric dimethylurate.

$$BaC_5(CH_3)_2N_4O_3 . 3 H_2O.$$
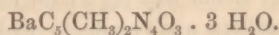
Dimethyluric acid was dissolved in as little boiling water as possible, a solution of baric hydrate added in slight excess of the amount

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theoretically required, and the solution boiled. The salt separated as the solution cooled, and was purified by recrystallization from hot water. It was filtered rapidly and dried in vacuo over sulphuric acid and potassic hydrate. The salt is quite soluble in hot, but slightly soluble in cold water. When cooled rapidly, it forms a jelly-like mass; but when cooled slowly, it crystallizes in flat, transparent prisms.

0.2177 gr. salt dried in vacuo gave 0.0307 gr. H_2O $= 14.10\%$
  Calculated for $BaC_5(CH_3)_2N_4O_3 . 3 H_2O$ . . . 14.03%
0.1875 gr. anhydrous salt gave 0.1335 gr. $BaSO_4$. Ba $= 41.86\%$
  Calculated for $BaC_5(CH_3)_2N_4O_3$ 41.89%

Monobaric dimethylurate.

$$Ba (C_5H(CH_3)_2N_4O_3)_2 . 3 H_2O.$$
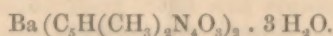
This salt was made by boiling an aqueous solution of the acid with baric carbonate, filtering, and precipitating the filtrate with alcohol.

0.3661 gr. salt dried in vacuo gave 0.0342 gr. H_2O $= 9.34\%$
  Calculated for $Ba (C_5H(CH_3)_2N_4O_3)_2 . 3 H_2O$. . 9.29%
0.3350 gr. anhydrous salt gave 0.1491 gr. $BaSO_4$. Ba $= 26.17\%$
  Calculated for $Ba (C_5H(CH_3)_2N_4O_3)_2$ 25.99%

Further study of the salts of dimethyluric acid seemed to us of no immediate importance, since the results we had reached served to establish beyond all doubt its dibasic character.

Action of Hydrochloric Acid.

Dimethyluric acid, when heated with concentrated hydrochloric acid, is completely decomposed, giving products perfectly analogous to those described by Strecker[*] as resulting from the decomposition of uric acid, and qualitatively identical with those obtained under the same conditions from methyluric acid.

The dimethyluric acid was heated for several hours with hydrochloric acid saturated at 0° to 170°. The liquid from the tubes, which showed great pressure on opening, was evaporated to dryness on the water-bath, the residue dissolved in water and distilled with plumbic hydrate in a current of steam as long as the distillate gave an alkaline reaction. The distillate was caught in hydrochloric acid, evap-

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[*] Ann. Chem. u. Pharm., exlvi. 142; Zeitschr. für Chemie, 1868, p. 215.

orated to dryness on the water-bath, and the residue treated with a mixture of absolute alcohol and ether. Ammonic chloride was left undissolved, while in solution was a salt which gave qualitative tests characteristic of the monamines. The platinum salt, recrystallized from water, gave on analysis: —

0.5421 gr. left on ignition 0.2261 gr. platinum.

	Calculated for $(CH_3NH_2)_2PtCl_6$.	Found.
Pt	41.61	41.75

In order to find the relative amounts of ammonia and methylamine which were formed in this reaction, we determined the percentage of chlorine in the saline residue as obtained by distillation with plumbic hydrate. The residue of chlorides was dried at 100° and the chlorine precipitated by argentic nitrate.

0.6365 gr. mixed chlorides gave 1.4681 gr. AgCl . $Cl_2 = 57.07\%$
Calculated for 2 molecules methylamine chloride
and 1 molecule ammonic chloride . . . . $= 56.50\%$

Two molecules of methylamine are therefore formed in the reaction and one molecule of ammonia.

The liquid remaining in the flask, after the distillation, was filtered hot, the lead precipitated as sulphide, and the filtered solution concentrated. On long standing crystals of glycocol separated, which, for identification, were converted into the copper salt by boiling with freshly precipitated cupric oxide, and precipitating the filtered solution with alcohol.
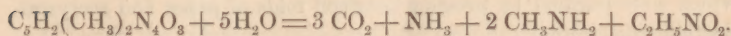
0.4757 gr. copper salt lost at 135° 0.0391 gr. H_2O.

	Calculated for $(C_2H_4NO_2)_2Cu . H_2O$	Found.
H_2O	7.85	8.22

0.4291 gr. anhydrous salt left on ignition 0.1611 gr. CuO.

	Calculated for $(C_2H_4NO_2)_2Cu$.	Found.
CuO	37.55	37.54

The reaction may therefore be written: —

$$C_5H_2(CH_3)_2N_4O_3 + 5H_2O = 3\ CO_2 + NH_3 + 2\ CH_3NH_2 + C_2H_5NO_2.$$

Oxidation of Methyluric Acid.

By the oxidation of dimethyluric acid with nitric acid we were unable to obtain a crystalline product. Since the crystalline amalic acid would undoubtedly have been formed had the two methyl radicals been attached to the same urea residue, we concluded that our sirupy oxidation product contained methylalloxan, and for its iden-

tification converted it at once into the calcic methylalloxanate. We followed closely the method which one of us had already described,* and found to give constant results. Dimethyluric acid was dissolved in the smallest possible quantity of nitric acid of sp. gr. 1.42, the solution diluted with water, and the excess of acid neutralized with calcic carbonate in the cold. After the solution was freed as nearly as possible from carbonic dioxide, by allowing it to stand for some time in vacuo, it was largely diluted with alcohol, filtered, and the calcic methylalloxanate precipitated by the cautious addition of ammonia. The carbon and hydrogen were estimated in this salt dried at 100° by a combustion in a stream of oxygen, the calcium by ignition with sulphuric acid.

I. 0.2334 gr. substance gave 0.2103 gr. CO_2, 0.0439 gr. H_2O, and 0.0921 gr. residue. This residue gave 0.1489 gr. $CaSO_4$, equivalent to 0.0611 gr. calcic oxide. The residue, therefore, contained 0.0311 gr. CO_2.

II. 0.2172 gr. gave 0.1401 gr. $CaSO_4$.

III. 0.2268 gr. gave 0.1448 gr. $CaSO_4$.

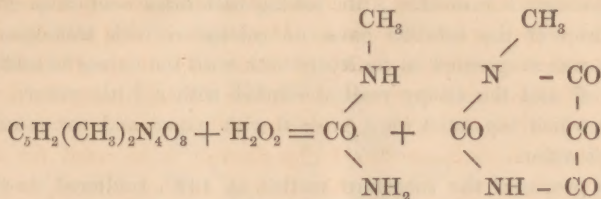|	Calculated for $C_4H(CH_3) . N_2O_5Ca$	Found. 1.	Found. 2.	Found. 3.
C	28.30	28.20		
H	1.88	2.09		
Ca	18.87	18.77	18.97	18.78

In confirmation of these results it seemed advisable to isolate the methylurea which should be formed as the second product of the reaction. We therefore oxidized with hydrochloric acid and potassic chlorate, according to the method of Schlieper, evaporated at a gentle heat until the greater part of the excess of hydrochloric acid was driven off, and then separated from the potassic chloride with absolute alcohol. The residue left by the evaporation of the alcohol at a low temperature gave with nitric acid crystals of methylurea nitrate, which were purified by pressing between folds of paper and recrystallization from water.

0.2464 gr. gave 0.1635 gr. CO_2 and 0.1147 gr. H_2O.

	Calculated for $C_2H_7N_3O_4$	Found.
C	17.81	18.09
H	5.11	5.15

* These Proceedings, Vol. XII. p. 38.

This reaction may therefore be written : —

$$
C_5H_2(CH_3)_2N_4O_3 + H_2O_2 =
\begin{array}{c}
CH_3 \\
| \\
NH \\
\diagup \quad \diagdown \\
CO \quad\quad NH_2 \\
\end{array}
\; + \;
\begin{array}{c}
CH_3 \\
\diagup \\
N \\
\diagup \quad \diagdown \\
CO \quad\quad NH \\
\end{array}
\;
\begin{array}{c}
- \; CO \\
| \\
CO \\
| \\
- \; CO \\
\end{array}
$$

By the oxidation with potassic chlorate we have, however, invariably observed the formation of a small quantity of a crystalline substance, which we have as yet been unable to obtain in sufficient quantity for investigation.. When the residue obtained by evaporation after oxidation was diluted with water, well-formed transparent prisms, pointed at either end, gradually separated, which could be recrystallized from hot water. The quantity formed was extremely small, and, although we modified the process in many ways, we have thus far been unable to increase the yield. At present, therefore, we can do no more than describe the few experiments we have been able to make with the small quantity at our disposal. The substance was readily soluble in hot water, sparingly soluble in cold water or in alcohol. In concentrated nitric acid it dissolved on warming, and crystallized out apparently unchanged on cooling. With ammonia it gave no red color. On heating it melted at about 160°. An analysis gave numbers which correspond more nearly with those required by $C_5H_6N_2O_3$ than by any other simple formula.

0.2078 gr. gave 0.3259 gr. CO_2 and 0.0788 gr. H_2O.

0.1459 gr. gave 25.6 cc. nitrogen at 16° and 720 mm. pressure.

	Calculated for $C_5H_6N_2O_3$	Found.
C	42.26	42.77
H	4.23	4.21
N	19.72	19.27

Although the substance possessed acid properties, we were unable to prepare its salts. On boiling with a solution of baric hydrate it was decomposed with the separation of baric carbonate. In the distillate the presence of ammonia and an amine, without doubt methylamine, could be proved by qualitative tests, and in the residue was an acid whose barium and lead salts were sparingly soluble in water, but which we were unable to identify on account of our very limited supply of material.

By the long-continued action of nitric acid upon dimethyluric acid methylparaban is formed. After boiling with nitric acid of sp. gr. 1.3 till a drop of the solution gave no coloration with ammonia, the solution was evaporated on the water-bath until the excess of acid was driven off and the sirupy residue diluted with a little water. The crystals which separated were pressed with paper and recrystallized from hot water.

Thus prepared the substance melted at 149°, sublimed slowly at 100°, readily at higher temperatures, and gave on analysis the percentages corresponding to methylparaban.

0.2838 gr. gave 0.3886 gr. CO_2 and 0.0879 gr. H_2O.

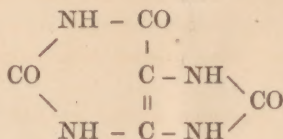|	Calculated for $C_3H(CH_3)N_2O_3$	Found.
C	37.50	37.35
H	3.13	3.45

By the oxidation of dimethyluric acid with potassic permanganate in alkaline solution, we have been unable to prepare the corresponding dimethylallantoin. The acid either undergoes a more radical decomposition, or more probably the assimilation of water takes place more readily than in case of allantoin or even methylallantoin and the dimethylallantoic acid results.

We made several attempts to isolate from the uncrystallizable product of the oxidation various salts of the dimethylallantoic acid, but found them so uninviting in their character, that we could hardly hope to effect their purification.
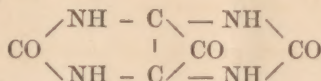

Since considerable time must of necessity elapse before further results can be obtained in this investigation, it may not be out of place to call attention to one inference concerning the structure of uric acid which may fairly be drawn from the facts thus far established.

It has been shown that the two hydrogen atoms of uric acid which are replaced in the formation of salts are directly connected with two different nitrogen atoms; furthermore, when methyl groups are introduced in the place of these hydrogen atoms, that two other hydrogen atoms may then be replaced by metals. The only simple explanation of this behavior would seem to be that the four hydrogen atoms of uric acid are attached to four different nitrogen atoms, and that only two of these hydrogen atoms can be replaced at the same time

by strongly basic radicals. Of the many structure-formulæ which have thus far been proposed for uric acid only two contain this arrangement of the hydrogen atoms. These are the formulæ of Medicus, * —

$$
\begin{array}{c}
NH - CO \\
\diagup \quad\quad | \\
CO \quad\quad\quad C - NH \\
\diagdown \quad\quad || \quad\quad\quad CO \\
NH - C - NH \diagup
\end{array}
$$

and of Fittig,† —

$$
\begin{array}{c}
\diagup NH - C \diagdown - NH \diagdown \\
CO \quad\quad | \quad CO \quad\quad CO \\
\diagdown NH - C \diagup - NH \diagup
\end{array}
$$

Further discussion of these formulæ, or of others fulfilling the same conditions, must be reserved for a subsequent paper.

<div align="right">H. B. H.</div>

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* Ann. Chem. u. Pharm., clxxv. 243.
† Grundniss. der Organischen Chemie, 10th edition, p. 309.